REMARKS

Claims 1-20 are pending in the instant application. Claims 10-20 have been withdrawn from consideration. Claims 1-9 have been rejected. Claims 3, 10-20 have been canceled. Claims 1, 2, 7 and 8 have been amended.

Amendments to the specification and Figures have been made to incorporate SEQ ID NO to sequences listed in the text. Accordingly, replacement sheets have been provided for both the Sequence listing and the Formal Drawings.

Moreover, lines 27 and 28 of page 11 have been amended as the three letter and one letter codes were inconsistent. Support for this amendment may be found on page 11 and at the website cited on page 11, lines 13 and 14. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Election/Restriction Requirement Under 35 U.S.C. §121

The restriction requirement placing the claims into Groups I-IV has been deemed proper and made final. Claims 10-20 are withdrawn from further consideration. Accordingly, Applicants are canceling claims 10-20 without prejudice, reserving the right to file continuing applications for the cancelled subject matter.

II. Priority Under 35 U.S.C. 119(e)

Applicants appreciate acknowledgement of priority to U.S. Provisional Patent Application Serial No. 60/132,358, filed May 4, 1999, under 35 U.S.C. 119(e).

III. Drawings and Sequence Compliance

The drawings have been accepted by the Examiner for examination purposes only. However, the Examiner indicates that the specification and Figures do not make reference to a SEQ ID NO as required under 37 U.S.C. §1.821(d).

Accordingly, Applicants have amended the specification and the formalized the replacement figures to comply with 37 U.S.C. §1.821(d).

IV. Rejection of Claims Under 35 U.S.C. §112

Claims 1, and 4-8 have been rejected under 35 U.S.C. §112, first paragraph, as the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. The Examiner suggests that while the specification is enabling for a chimeric protein comprising a β-glucuronidase linked to a hormone binding domain by a peptide comprising a spacer sequence and a caspase cleavage site wherein the β-glucuronidase is inactive due to the linkage to the linkage to the hormone binding domain and the release of the β-glucuronidase through caspase cleavage of the cleavage site restores the enzyme activity of β-glucuronidase, it does not reasonably provide enablement for such a fusion protein comprising any reporter and any repressor linked through a protease (caspase) cleavage sequence or such fusion proteins comprising a plurality of reporter and repressor domain linked by more than one type of caspase cleavage linkers.

Specifically, the Examiner suggests that while the specification teaches that a hormone binding domain of a steroid

receptor can act as a repressor of β-glucuronidase, the specification is totally silent as to the repressors for all or any other types of enzymes that those skilled in the art would choose. Thus, in view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the Examiner suggests that undue experimentation is required. Moreover, the Examiner suggests that the specification does not support the broad scope of the claims because the specification does not establish: A) a universal list of all the reporters and their specific repressors; and B) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicants respectfully traverse this rejection.

In an effort to advance the prosecution of this application, Applicants have amended claim 1 to recite that the reporter domain comprises β-glucuronidase as this reporter protein is shown to be inactivated by a repressor domain. Accordingly, claim 3 has been canceled. Applicants believe that the specification clearly discloses cellular receptor repressor domains (page 9, line 15 to page 10, line 28) such as those of steroid hormone receptors and bHLH/PAS superfamily of transcription regulators which may be used in combination with β-glucuronidase. Such cellular receptor repressor domains provided in the specification are well-established in the art for their use in repressing activity of a protein in close proximity. Thus, one of skill would be able to prepare a chimeric protein in accordance with the invention using such repressor domains in combination with β-

glucuronidase with the guidance provided by the specification. MPEP 2164.01 states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. Denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrick GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1, and 4-8 have also been rejected under U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, the Examiner suggests that no information beyond the characterization of the function (β-glucuronidase and it repressor, hormone binding domain) of a single species was provided by the specification to indicate that Applicants were in possession of chimeric polypeptides comprising any reporter and repressor. The Examiner suggests that the specification does not provide a structure and function of all the polypeptide sequences, including fragments and variants, within the scope of the claimed genus

Applicants respectfully traverse this rejection.

The specification clearly provides an exemplary β-glucuronidase which may be used in a chimeric polypeptide of amended claim 1 and by dependency, claims 4-8. As indicated *supra*, cellular receptor repressor domains are well-known to one of skill in the art. There are numerous publications and GENBANK entries which recite the sequences of repressor domains disclosed in the instant application as well as variants which retain the desired functional activity recited in the claims (*i.e.*, repressing activity of a normally biologically active protein fused thereto). For example, Mattioni et al. ((1994) *Methods in Cell Biology,* Vol. 43:335-, page 341, third paragraph) provides additional citations and variants of cellular receptor repressor domains. Thus, the skilled artisan could readily obtain these known sequences with the known functions in view of the specification to generate a chimeric protein of the invention. Accordingly, withdrawal of this rejection is respectfully requested.

V. Rejection of Claims Under 35 U.S.C. §102

Claims 1, and 4-5 have been rejected under 35 U.S.C. §102(a) as being clearly anticipated by Hawkins et al. ((March 1999) *Proc. Natl. Acad. Sci.* 96:2885-2890). The Examiner suggests that Hawkins et al. teach the instant invention as this reference discloses a chimeric protein comprising CLBDG6 (CD4 trans-membrane domain) linked to the transcription factor domain through a linker sequence comprising a caspase cleavage site and a spacer. The CLBDG6 acts as a repressor of the transcription domain by translocating it to the cell membrane as opposed to its biological function in the nucleus as a transcription factor

wherein the cleavage by a protease such as the caspase releases it from the membrane and allows it to function normally as a transcription factor.

Claims 1, and 4-5 are further rejected under 35 U.S.C. §102(b) as being clearly anticipated by Xu et al. ((1998) *Nucl. Acids. Res.* 26(8):2034-2035). The Examiner suggests that Xu et al. teach the instant invention as this reference discloses a chimeric protein comprising the GFP and BFP linked together through a linker comprising a spacer and a caspase cleavage sequence. The two fluorescent proteins both act as reporters and repressors of each other and thus when in close proximity reduce the fluorescence intensity compared to the intensity of the individual protein. Cleavage by caspase eliminates the reduction in fluorescence.

Applicants respectfully traverse this rejection.

To further the prosecution of the instant application, applicants have amended claims 1 and 2 to recite that the reporter is β-glucuronidase and that the repressor domain is taken from a cellular receptor as indicated on pages 9 and 10 of the application. Thus, as neither Hawkins et al. nor Xu et al. teach each and every element of the claimed invention (*i.e.*, a chimeric protein comprising a cellular receptor repressor domain fused to β-glucuronidase), they do not anticipate it. It is therefore respectfully requested that these objections be withdrawn.

VI. Rejection of Claims Under 35 U.S.C. §103

Claims 2-3 and 9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Xu et al. or Hawkins et al. as applied

to claims 1, and 4-5 *supra,* and further in view of Mattioni et al. The Examiner acknowledges that neither Hawkins et al. nor Xu et al. teach fusion proteins comprising a HBD wherein the reporter part of the fusion protein is rendered inactive because of its fusion to the HBD or that the reporter is rendered active upon cleavage of the HBD by a protease.

The Examiner suggests that Mattioni et al. teach regulation of protein activities by fusion to steroid binding domains and that an alternate method to inducible expression of a protein activity can be developed by making a fusion protein, comprising the protein of interest whose activity needs to be controlled (*i.e.,* reporter domain) and a HBD sequence linked to the N-terminal or C-terminal of the reporter protein wherein steric hinderance created by the HBD renders the reporter inactive. The Examiner further suggests that with these references in hand it would have been obvious to one of ordinary skill in the art to combine the teachings and arrive at a fusion protein as recited by claims 2-3 and 9 and that one would have been motivated to do so as Mattioni et al. provide an easy, yet robust method of modulating the activity of a protein and Xu et al. and Hawkins et al. teach the method of using fusion proteins comprising protease cleavage sites for determining the presence of specific proteases. Further, the Examiner suggests that one of ordinary skill in the art would have had a reasonable expectation of success since the above references teach all the important aspects of the invention.

Applicants respectfully traverse this rejection.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must

be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As acknowledged by the Examiner, the primary references of Hawkins et al. and Xu et al. do not teach fusion proteins comprising a HBD wherein the reporter part of the fusion protein is rendered inactive because of its fusion to the HBD or that the reporter is rendered active upon cleavage of the HBD by a protease. Further, these references as well as Mattioni et al. fail to suggest or motivate one of skill in the art to modify the teachings in the art to provide a HBD domain linked via a protease cleavage site to a reporter such that the reporter is inactive until the HBD domain is cleaved from the reporter by a protease which recognizes the protease cleavage site. Applicants respectfully disagree with the Examiner's suggestion that Mattioni et al. provide the motivation to combine the references as this references teaches an easy, yet robust, method of modulating the activity of a protein. Applicants believe that the teachings of Mattioni et al. in fact would dissuade the skilled artisan from combining the cited references for the fact that this reference teaches an easy and robust method for modulating the activity of a reporter; there would be little motivation to

modify the fusion proteins taught by this reference to incorporate yet another element such a protease cleavage site. It is only in view teachings of the instant application that one of skill would be motivated to combine the teachings of the cited references to arrive at the instant inventive fusion proteins. It is therefore respectfully requested that this rejection be withdrawn.

Claims 6-8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Xu et al. or Hawkins et al. as applied to claims 1, and 4-5 *supra,* and further in view of the common knowledge in the art.

The Examiner suggests that using the teachings of Xu et al. and Hawkins et al., it would have been obvious to those skilled in the art to have multiple reporter domains such that the signal intensity obtained from the reporter domain, whether via fluorescence as in Xu et al. or via the transcription of a detector gene as in the case of Hawkins et al. would be more intense and its detection be easier. The Examiner further suggests that because of the simplicity and ease of use of the technique it would have been obvious to one of skill in the art to use multiple protease cleavage sites and detect the presence of multiple sets of proteases. The Examiner indicates that Xu et al. and Hawkins et al. provide the motivation to do so as these references disclose a robust and simple method for detecting a single type of protease using a chimeric protein comprising a single reporter, a single repressor and a single protease cleavage site.

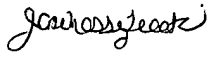
Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiners suggestion that claims 6-8 are obvious in light of the teachings of Xu et al. and Hawkins et al. As set forth by both the Court of Appeals for the Federal Circuit and the MPEP, when an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and MPEP § 2143.03. As indicated *supra*, Xu et al. and Hawkins et al. in view of Mattioni et al. fail to teach, suggest, or motivate the skilled artisan to combine the teachings of the cited references to arrive at the instant inventive fusion as set forth in independent claim 1. Accordingly, the cited combinations of prior art references can not render obvious the instant claimed invention. Withdrawal of these rejections is therefore respectfully requested.

VII. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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